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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/248,382	02/10/1999	RAMA MUKHERJEE	U012104-2	8689

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EXAMINER
MOHAMED, ABDEL A

ART UNIT	PAPER NUMBER
1653	17

DATE MAILED: 03/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/248,382	Applicant(s) MUKHERJEE ET AL.	
	Examiner Abdel A. Mohamed	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 32-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 32-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

ACKNOWLEDGMENT OF THE AMENDMENT, REMARKS AND STATUS OF THE CLAIMS

1. The amendment and remarks filed 12/7/01 are acknowledged, entered and considered. In view of Applicant's request claim 1 has been amended. Thus, claims 1-4 and 32-36 are now pending in the application. The rejection under 35 U.S.C. 112, first paragraph, the objection to the specification partially and 35 U.S.C. 112, second paragraph partially are withdrawn in view of Applicant's amendment and response filed 12/7/01. However, the objection to the specification partially, the rejection under 35 U.S.C. 112, second paragraph partially and 35 U.S.C. 103(a) over the prior art of record are maintained.

2. The text of those sections of Title 35, U.S.C. Code not included in this action can be found in a prior Office action.

ARGUMENTS ARE NOT PERSUASIVE

OBJECTION TO THE SPECIFICATION

3. Applicant's arguments filed 12/7/01 have been fully considered but they are not persuasive.

The objection of the specification with respect to the definition for Dxg includes Aib is withdrawn in view of Applicant's arguments. However, the objection of the specification in regard to "in our previous studies" is maintained for the same reasons of record. It is noted that

Applicant has amended page 1, paragraph 5 by adding "now U.S. Patent No. 6,156,725"; however, it is still unclear if the phrase "previous studies" objected by the Examiner in the instant specification on page 2, line 31; page 3, line 25; page 4, lines 14 and 31 and page 5, line 10, for example would reflect to the above recited patent or other "previous studies". Thus, appropriate clarification is required. Further, Applicant's amendment filed 12/7/01, on page 2, line 1 discloses "MUJ-&". It is believed to be typographical error. Appropriate correction is suggested.

CLAIMS REJECTION-35 U.S.C. § 112[2nd] PARAGRAPH

4. The rejection of claims 1-4 and 32-36 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is noted that Applicant has amended independent claim 1 partially as suggested by the Examiner, rendering the rejection pertaining thereto moot. Thus, the rejection for the claim which has been amended according to the Examiner's suggestion has been withdrawn, but, issues in the claim which have not been amended and have been argued by Applicant are maintained for the same reasons discussed on the previous Office action. Applicant has argued that the term "Dxg" does not need to be defined in the claims since it si defined in the specification is unpersuasive because the definiteness of the claim is important to allow others who wish to enter the market place to ascertain the boundaries of protection that are provided by the claims. See *Ex parte Kristensen,* 10 USPQ 2d. 1701, 1703 (PTO Bd. App. & Inter. 1989). Hence, in order to obviate

the above rejection, it is suggested again that Applicant amend the claim to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

CLAIMS REJECTION-35 U.S.C. § 103(a)

5. The rejection of claims 1-4 and 32 34 under 35 U.S.C. 103(a) as being unpatentable over Gozes et al. (U.S. Patent No. 5,217,853) in view of Spatola (Chemistry and Biochemistry of Amino Acids, Peptides and Proteins, Chapter 5, page 271, 1983).

Applicant has argued that Spatola teaches substitution of D amino acids for L amino acids. Spatola is a review paper and there is nothing in Spatola that discloses that the amino acids of VIP can be modified or replaced. Although, Spatola discloses use of D amino acids and Aib, there is no disclosure or suggestion in Gozes or Spatola of the particular peptides claimed in this specification. Further, Applicant states that Spatola lists 22 types of modifications that can be made to a peptide. Given the numerous options provided in Spatola, the only basis for the Examiner's rejection is hindsight because there is no suggestion in either reference to modify VIP with Dxg or Aib residues is noted.

However, Applicant's argument is unpersuasive for the reasons of record. The Examiner has clearly shown that the primary reference of Gozes et al. teaches that VIP antagonists are known and used to treat cancer. The amino acid sequence of claim 1 (SEQ ID NO:1) and use thereof is also taught by this reference. However, the primary reference does not teach the modified peptides as claimed. Nevertheless, the secondary reference of Spatola teaches that the

modified peptides exhibit resistance toward enzyme degradation. Spatola further teaches how the various modifications in a peptide sequence alter the properties of the thus modified resulting peptides, such as substitution of a D amino acid for an L amino acid in a peptide sequence. Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to modify the peptides of the primary reference of Gozes et al. according to the secondary reference of Spatola's teachings to obtain stability and enzyme degradation resistance (i.e., to survive passage through the gut) at the time the invention as made.

Therefore, contrary to Applicant's argument, given the teachings of the secondary reference, one of ordinary skill in the art would have been motivated to adapt the above scheme of modifying the peptides as claimed (i.e., substitution of D amino acid for L amino acid in a peptide sequence) for treating cancer, because such features are known in the art. Hence, including such features into the polypeptide of the primary reference in view of the secondary reference, would have been obvious to one having ordinary skill in the art to obtain the known and recognized functions and advantages thereof. Thus, in view of this, the subject composition may be used in combination with other materials to provide a wide variety of applications or may be tailored for specific applications. Therefore, it is made obvious by the combined teachings of the prior art since the instantly claimed invention which falls within the scope of the prior art teachings would have been obvious because as held in host of cases including *Ex parte Harris*, 748 O.G. 586; *In re Rosselete*, 146 USPQ 183; *In re Burgess*, 149 USPQ 355 and as exemplified by *In re Betz*, "the test of obviousness is not express suggestion of the claimed invention in any and all of the

references but rather what the references taken collectively would suggest to those of ordinary skill in the art presumed to be familiar with them".

The following is a new ground of rejection

NEW GROUND OF REJECTION

CLAIMS REJECTION-35 U.S.C. 112 [1st] PARAGRAPH.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 32-36 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the preparation of peptide composition comprising peptide analogs of vasoactive intestinal peptide (VIP), somatostatin (SOM), bombesin (BOM) and Substance P and peptides of SEQ ID NOS:1-27 and using the above peptides individually or in combination *in vitro* to inhibit the proliferation or growth of tumor cells, does not reasonably provide enablement for a therapeutically effective pharmaceutical composition containing either individual peptides or in combination for *in vivo* treatment of various cancers in patients and to methods of treatment thereof as recited in claims 1-4 and 32-36. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims; e.g., claims 1-2 are

directed to compositions and claims 3-4 and 32-36 are directed to "*in vivo*" "treatment" of various cancers using the compositions of claims 1-2 as presently claimed without qualifiers.

The instant specification on pages 2-5 teaches how to prepare the combination of twenty seven peptides peptide analogs of SEQ ID NOS:1-27. Also, Example 1 teaches the testing of the cytotoxic activity of the various tumor cell lines *in vitro*, Tables I-V demonstrate the percentages of cytotoxicity of the synthesized peptides on various tumor cell lines and Example 2 and Tables VI-VII show the percentage increase of half-life of the peptides synthesized as estimated by the mouse liver homogenate study. However, the scope of the instantly claimed invention are very broad and speculative in that there is no working example or data or evidence which shows that the claimed peptides individually or in combination are useful as a pharmaceutical composition by administering as an active ingredient a therapeutically effective amount of the peptide to treat the various cancers in patients such as cancers of the colon, breast, ovary, lung, prostate, or leukemia as claimed in claims 3-4 and 32-36.

There is no evidence in the instant specification to use or administer the pharmaceutical formulation in therapeutically effective composition as claimed. There is no dosage amount for pharmaceutical composition disclosed, except for the various *in vitro* assays which show the percentages and activities of cytotoxicity of various tumor cell lines *in vitro* on treatment with different concentrations of peptides and analogs as disclosed in Examples 1-2 and Tables I-VII. Thus, there are no sufficient data or evidence to substantiate such protocols of using a therapeutically effective pharmaceutical composition for treating all kinds of cancers in the

manner claimed. Hence, the only support for the claimed therapeutically effective pharmaceutical composition and method of treatment of cancers in patients by administering a therapeutically effective dose of the pharmaceutical composition thereof in the specification is Applicant's supposition of the invention as recited in the protocols. Furthermore, Applicant's claims are directed to a very large number of compounds by using specific therapeutically effective amount of pharmaceutical composition, and there are no objective factual evidence in the specification showing that treatment of cancer has occurred using the specific therapeutically effective amount of pharmaceutical composition claimed. Thus, it is the Examiner's position that one can not administer specific effective amount of a pharmaceutical composition in all situations without appropriate testing which would require the exercise of undue experimentation, as for example, treating *in vivo* the various cancers claimed.

Therefore, in view of the above, it would include those that have not been shown or taught to be useful or enabled by the disclosed method of making and using the invention. Moreover, undue experimentation is necessary to determine if and under what conditions, the claimed invention as broadly claimed is enabled, since a vast range of pharmaceutical composition in all kinds of possible compounds are contemplated and are encompassed as well as wide range of situations. The results desired appear to be highly dependent on all variables, the relationship of which are not present in the specification. Hence, one of ordinary skill in the art would not be able to identify all the pharmaceutical preparations with the various peptides either alone or in

combination having all kinds of concentrations intended to be effective for the claimed purpose as encompassed in the claims would be effective and under what conditions.

Further, the first paragraph of 35 U.S.C. 112 requires, inter alia, that a patent specification provide sufficient guidance to enable a person skilled in the art to make and use the claimed invention without undue experimentation. In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991). While patent Applicants are not directed to disclose every species that falls within a generic claim, id. At 496, 20 USPQ2d at 1445, it is well settled that "the scope of the claims must bear a reasonable correlation to the scope of the enablement provided by the specification". In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Where practice of the full scope of the claims would require experimentation; factors to be considered in determining whether a disclosure would require undue experimentation ..... include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. In re Wands, 858 F. 2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Therefore, applying the Wands factors to the facts of this case, one of skill in the art would find that undue amount of experimentation would be required to practice the full scope of the extremely broad claims fro the reasons given above. Thus, in view of the quantity of experimentation necessary, the lack of adequate guidance or working examples or data. and the

breadth of the claims, the claims are not commensurate in scope with the enabling disclosure. Accordingly, filing of evidence commensurate with the scope of the claims or amendment of the claims to what is supported by the enabling disclosure is suggested.

CONCLUSION AND FUTURE CORRESPONDENCE

7. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Abdel A. Mohamed whose telephone number is (703) 308-3966. The examiner can normally be reached on Monday through Friday from 5:30 a.m. to 5:00 p.m. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached on (703) 308-2923. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

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